

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-966/S-001, S-003, S-004

20-657/S-004, S-005

APPROVED DRAFT LABELING

SPORANOX[®]
(ITRACONAZOLE)
ORAL SOLUTION

Congestive Heart Failure: When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. If signs or symptoms of congestive heart failure occur during administration of SPORANOX[®] (itraconazole) Oral Solution, continued SPORANOX[®] use should be reassessed. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Post-marketing Experience for more information.)

Drug Interactions: Coadministration of cisapride, pimozide, quinidine, or dofetilide with SPORANOX[®] (itraconazole) Capsules, Injection or Oral Solution is contraindicated. SPORANOX[®], a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, or quinidine, concomitantly with SPORANOX[®] and/or other CYP3A4 inhibitors. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.

DESCRIPTION

SPORANOX[®] is the brand name for itraconazole, a synthetic triazole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following structural formula and nomenclature:

(insert structure)

(±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[(2R*,4S*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ²-1,2,4-triazolin-5-one mixture with (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[(2S*,4R*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ²-1,2,4-triazolin-

5-one

or

(±)-1-[(RS)-sec-butyl]-4-[p-[4-[p-[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ²-1,2,4-triazolin-5-one.

Itraconazole has a molecular formula of C₃₅H₃₈Cl₂N₈O₄ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

SPORANOX® (itraconazole) Oral Solution contains 10 mg of itraconazole per mL, solubilized by hydroxypropyl-β-cyclodextrin (400 mg/mL) as a molecular inclusion complex. SPORANOX® Oral Solution is clear and yellowish in color with a target pH of 2. Other ingredients are hydrochloric acid, propylene glycol, purified water, sodium hydroxide, sodium saccharin, sorbitol, cherry flavor 1, cherry flavor 2 and caramel flavor.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism: NOTE: The plasma concentrations reported below were measured by high-performance liquid chromatography (HPLC) specific for itraconazole. When itraconazole in plasma is measured by a bioassay, values reported may be higher than those obtained by HPLC due to the presence of the bioactive metabolite, hydroxyitraconazole. (See MICROBIOLOGY.)

The absolute bioavailability of itraconazole administered as a non-marketed solution formulation under fed conditions was 55% in 6 healthy male volunteers. However, the bioavailability of SPORANOX® (itraconazole) Oral Solution is increased under fasted conditions reaching higher maximum plasma concentrations (C_{max}) in a shorter period of time. In 27 healthy male volunteers, the steady-state area under the plasma concentration versus time curve (AUC_{0-24h}) of itraconazole (SPORANOX® Oral Solution, 200 mg daily for 15 days) under fasted conditions was 131 ± 30% of that obtained under fed conditions. Therefore, unlike SPORANOX® Capsules, it is recommended that SPORANOX® Oral Solution be administered without food. Presented in the table below are the steady-state (Day 15) pharmacokinetic parameters for itraconazole and hydroxyitraconazole (SPORANOX® Oral Solution) under fasted and fed conditions:

	Itraconazole		Hydroxyitraconazole	
	Fasted	Fed	Fasted	Fed
C_{max} (ng/mL)	1963 ± 601*	1435 ± 477	2055 ± 487	1781 ± 397
T_{max} (hours)	2.5 ± 0.8	4.4 ± 0.7	5.3 ± 4.3	4.3 ± 1.2
AUC_{0-24h} (ng·h/mL)	29271 ± 10285	22815 ± 7098	45184 ± 10981	38823 ± 8907
$t_{1/2}$ (hours)	39.7 ± 13	37.4 ± 13	27.3 ± 13	26.1 ± 10

*mean ± standard deviation

The bioavailability of SPORANOX® Oral Solution relative to SPORANOX® Capsules was studied in 30 healthy male volunteers who received 200 mg of itraconazole as the oral solution and capsules under fed conditions. The $AUC_{0-\infty}$ from SPORANOX® Oral Solution was 149 ± 68% of that obtained from SPORANOX® Capsules; a similar increase was observed for hydroxyitraconazole. In addition, a cross study comparison of itraconazole and hydroxyitraconazole pharmacokinetics following the administration of single 200 mg doses of SPORANOX® Oral Solution (under fasted conditions) or SPORANOX® Capsules (under fed conditions) indicates that when these two formulations are administered under conditions which optimize their systemic absorption, the bioavailability of the solution relative to capsules is expected to be increased further. Therefore, it is recommended that SPORANOX® Oral Solution and SPORANOX® Capsules not be used interchangeably. The following table contains pharmacokinetic parameters for itraconazole and hydroxyitraconazole following single 200 mg doses of SPORANOX® Oral Solution (n=27) or SPORANOX® Capsules (n=30) administered to healthy male volunteers under fasted and fed conditions, respectively:

	Itraconazole		Hydroxyitraconazole	
	Oral Solution fasted	Capsules fed	Oral Solution fasted	Capsules fed
C_{max} (ng/mL)	544 ± 213*	302 ± 119	622 ± 116	504 ± 132
T_{max} (hours)	2.2 ± 0.8	5 ± 0.8	3.5 ± 1.2	5 ± 1
AUC_{0-24h} (ng·h/mL)	4505 ± 1670	2682 ± 1084	9552 ± 1835	7293 ± 2144

*mean ± standard deviation

The plasma protein binding of itraconazole is 99.8% and that of hydroxyitraconazole is 99.5%. Following intravenous administration, the volume of distribution of itraconazole averaged 796 ± 185 L.

Itraconazole is metabolized predominately by the cytochrome P450 3A4 isoenzyme system (CYP3A4), resulting in the formation of several metabolites, including hydroxyitraconazole, the major metabolite. Results of a pharmacokinetics study suggest that itraconazole may undergo saturable metabolism with multiple dosing. Fecal excretion of the parent drug varies between 3-18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 40% of the dose is excreted as inactive metabolites in the urine. No single excreted metabolite represents more than 5% of a dose. Itraconazole total plasma clearance averaged 381 ± 95 mL/minute following intravenous administration. (See CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions for more information.)

Special Populations:

Pediatrics: The pharmacokinetics of SPORANOX® Oral Solution were studied in 26 pediatric patients requiring systemic antifungal therapy. Patients were stratified by age: 6 months to 2 years (n=8), 2 to 5 years (n=7) and 5 to 12 years (n=11), and received itraconazole oral solution 5 mg/kg once daily for 14 days. Pharmacokinetic parameters at steady-state (Day 14) were not significantly different among the age strata and are summarized in the table below for all 26 patients:

	Itraconazole	Hydroxyitraconazole
C _{max} (ng/mL)	582.5 ± 382.4*	692.4 ± 355.0
C _{min} (ng/mL)	187.5 ± 161.4	403.8 ± 336.1
AUC _{0-24h} (ng·h/mL)	7706.7 ± 5245.2	13356.4 ± 8942.4
t _{1/2} (hours)	35.8 ± 35.6	17.7 ± 13.0

*mean ± standard deviation

Renal Insufficiency: A pharmacokinetic study using a single 200-mg dose of itraconazole (four 50-mg capsules) was conducted in three groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of 13 mL/min. x 1.73 m², the bioavailability was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole (T_{max}, C_{max}, and AUC₀₋₈). Plasma concentration-versus-time profiles showed wide intersubject variation in all three groups.

Hepatic Insufficiency: Patients with impaired hepatic function should be carefully monitored when taking itraconazole. The prolonged elimination half-life of itraconazole observed in cirrhotic patients should be considered when deciding to initiate therapy with other medications metabolized by CYP3A4. (See BOX WARNING, CONTRAINDICATIONS, and PRECAUTIONS: Drug Interactions.)

Decreased Cardiac Contractility: When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of SPORANOX[®] Injection (intravenous infusion), transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later. If signs or symptoms of congestive heart failure appear during administration of SPORANOX[®] Oral Solution, monitor carefully and consider other treatment alternatives which may include discontinuation of SPORANOX[®] Oral Solution administration. (See WARNINGS, PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Post-marketing Experience for more information.)

MICROBIOLOGY

Mechanism of Action: In vitro studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

Activity In Vitro and In Vivo: Itraconazole exhibits in vitro activity against *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Histoplasma duboisii*, *Aspergillus flavus*, *Aspergillus fumigatus*, *Candida albicans*, and *Cryptococcus neoformans*. Itraconazole also exhibits varying in vitro activity against *Sporothrix schenckii*, *Trichophyton* species, *Candida krusei*, and other *Candida* species. The bioactive metabolite, hydroxyitraconazole, has not been evaluated against *Histoplasma capsulatum* and *Blastomyces dermatitidis*. Correlation between minimum inhibitory concentration (MIC) results in vitro and clinical outcome has yet to be established for azole antifungal agents.

Itraconazole administered orally was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Fungistatic activity has been demonstrated against disseminated fungal infections caused by *Blastomyces dermatitidis*, *Histoplasma duboisii*, *Aspergillus fumigatus*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*.

Itraconazole administered at 2.5 mg/kg and 5 mg/kg via the oral and parenteral routes increased survival rates and sterilized organ systems in normal and immunosuppressed guinea pigs with disseminated *Aspergillus fumigatus* infections. Oral itraconazole administered daily at 40 mg/kg and 80 mg/kg increased survival rates in normal rabbits with disseminated disease and in immunosuppressed rats with pulmonary *Aspergillus fumigatus* infection, respectively. Itraconazole has demonstrated antifungal activity in a variety of animal models infected with *Candida albicans* and other *Candida* species.

Resistance: Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated in vitro and from patients receiving prolonged therapy.

Several in vitro studies have reported that some fungal clinical isolates, including *Candida* species, with reduced susceptibility to one azole antifungal agent may also be less susceptible to other azole derivatives. The finding of cross-resistance is dependent on a

number of factors, including the species evaluated, its clinical history, the particular azole compounds compared, and the type of susceptibility test that is performed. The relevance of these in vitro susceptibility data to clinical outcome remains to be elucidated.

Studies (both in vitro and in vivo) suggest that the activity of amphotericin B may be suppressed by prior azole antifungal therapy. As with other azoles, itraconazole inhibits the ¹⁴C-demethylation step in the synthesis of ergosterol, a cell wall component of fungi. Ergosterol is the active site for amphotericin B. In one study the antifungal activity of amphotericin B against *Aspergillus fumigatus* infections in mice was inhibited by ketoconazole therapy. The clinical significance of test results obtained in this study is unknown.

CLINICAL STUDIES

Empiric Therapy in Febrile Neutropenic Patients: An open randomized trial compared the efficacy and safety of itraconazole (intravenous followed by oral solution) with amphotericin B for empiric therapy in 384 febrile, neutropenic patients with hematologic malignancies who had suspected fungal infections. Patients received either itraconazole (injection, 200 mg BID for 2 days followed by 200 mg once daily for up to 14 days, followed by oral solution, 200 mg BID) or amphotericin B (total daily dose of 0.7-1.0 mg/kg body weight). The longest treatment duration was 28 days. An outcome assignment of "success" required (a) patient survival with resolution of fever and neutropenia within 28 days of treatment, (b) absence of emergent fungal infections, (c) no discontinuation of therapy due to toxicity or lack of efficacy, and (d) treatment for three or more days. The success rate using an intent-to-treat analysis was 47% for the itraconazole group and 38% for the amphotericin B arm.

**Overview of Efficacy
(Intent-to-Treat Population)**

Efficacy Parameters	SPORANOX N=179 (%)	Amphotericin B N=181 (%)
Success	84 (47%)	68 (38%)
Unevaluable*	24 (13%)	44 (24%)
Failure	71 (40%)	69 (38%)
Reason for Failure		
Intolerance after > 3 days of antifungal medication	12	37
Persistent fever	20	7
Change in antifungal medication due to fever	13	1
Emergent fungal infection	10	9
Documented bacterial or viral infection	7	8
Insufficient response	6	5
Deterioration of signs and symptoms	2	0
Death after > 3 days antifungal medication	1	2
Resolution of fever	131 (73%)	127 (70%)
Survival	161 (90%)	156 (86%)

* Treatment duration ≤ 3 days (including patients who died within 3 days, withdrew because of adverse events or were deemed ineligible due to a confirmed pre-treatment infection.)

Oropharyngeal Candidiasis: Two randomized, controlled studies for the treatment of oropharyngeal candidiasis have been conducted (total n=344). In one trial, clinical response to either 7 or 14 days of itraconazole oral solution, 200 mg/day, was similar to fluconazole tablets and averaged 84% across all arms. Clinical response in this study was defined as cured or improved (only minimal signs and symptoms with no visible lesions). Approximately 5% of subjects were lost to follow-up before any evaluations could be performed. Response to 14 days therapy of itraconazole oral solution was associated with a lower relapse rate than 7 days of itraconazole therapy. In another trial, the clinical response rate (defined as cured or improved) for itraconazole oral solution was similar to clotrimazole troches and averaged approximately 71% across both arms, with approximately 3% of subjects lost to follow-up before any evaluations could be performed. Ninety-two percent of the patients in these studies were HIV seropositive.

In an uncontrolled, open-label study of selected patients clinically unresponsive to fluconazole tablets (n=74, all patients HIV seropositive), patients were treated with itraconazole oral solution 100 mg b.i.d. (Clinically unresponsive to fluconazole in this study was defined as having received a dose of fluconazole tablets at least 200 mg/day for a

minimum of 14 days.) Treatment duration was 14-28 days based on response. Approximately 55% of patients had complete resolution of oral lesions. Of patients who responded and then entered a follow-up phase (n=22), all relapsed within 1 month (median 14 days) when treatment was discontinued. Although baseline endoscopies had not been performed, several patients in this study developed symptoms of esophageal candidiasis while receiving therapy with itraconazole oral solution. Itraconazole oral solution has not been directly compared to other agents in a controlled trial of similar patients.

Esophageal Candidiasis: A double-blind randomized study (n=119, 111 of whom were HIV seropositive) compared itraconazole oral solution (100 mg/day) to fluconazole tablets (100 mg/day). The dose of each was increased to 200 mg/day for patients not responding initially. Treatment continued for 2 weeks following resolution of symptoms, for a total duration of treatment of 3-8 weeks. Clinical response (a global assessment of cured or improved) was not significantly different between the two study arms, and averaged approximately 86% with 8% lost to follow-up. Six of 53 (11%) itraconazole-treated patients and 12/57 (21%) fluconazole-treated patients were escalated to the 200 mg dose in this trial. Of the subgroup of patients who responded and entered a follow-up phase (n=88), approximately 23% relapsed across both arms within 4 weeks.

INDICATIONS AND USAGE

SPORANOX® (itraconazole) Injection/Oral Solution is indicated for empiric therapy of febrile neutropenic patients with suspected fungal infections. (NOTE: In a comparative trial, the overall response rate for itraconazole-treated subjects was higher than for amphotericin B-treated subjects. However, compared to amphotericin B-treated subjects, a larger number of itraconazole-treated subjects discontinued treatment due to persistent fever and a change in antifungal medication due to fever. Whereas, a larger number of amphotericin B-treated subjects discontinued due to drug intolerance. See CLINICAL STUDIES section.)

SPORANOX® (itraconazole) Oral Solution is also indicated for the treatment of oropharyngeal and esophageal candidiasis.

(See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and ADVERSE REACTIONS: Post-marketing Experience for more information).

CONTRAINDICATIONS

Drug Interactions: Concomitant administration of SPORANOX[®] (itraconazole) Capsules, Injection, or Oral Solution and certain drugs metabolized by the cytochrome P450 3A4 isoenzyme system (CYP3A4) may result in increased plasma concentrations of those drugs, leading to potentially serious and/or life-threatening adverse events. Cisapride, oral midazolam, pimozide, quinidine, dofetilide and triazolam are contraindicated with SPORANOX[®]. HMG CoA-reductase inhibitors metabolized by CYP3A4, such as lovastatin and simvastatin, are also contraindicated with SPORANOX[®]. (See BOX WARNING, and PRECAUTIONS: Drug Interactions.)

SPORANOX[®] is contraindicated for patients who have shown hypersensitivity to itraconazole or its excipients. There is no information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used when prescribing SPORANOX[®] to patients with hypersensitivity to other azoles.

WARNINGS

SPORANOX[®] (itraconazole) Oral Solution and SPORANOX[®] Capsules should not be used interchangeably. Only SPORANOX[®] Oral Solution has been demonstrated effective for oral and/or esophageal candidiasis. SPORANOX[®] Oral Solution contains the excipient hydroxypropyl- β -cyclodextrin which produced pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings is unknown. (See Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

Hepatic Effects: SPORANOX[®] has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, the risks and benefits of continued SPORANOX[®] use should be reassessed. (See PRECAUTIONS: Information for Patients and ADVERSE EVENTS.)

Cardiac Dysrhythmias: Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using cisapride, pimozide or quinidine concomitantly with SPORANOX[®] and/or other CYP3A4 inhibitors. Concomitant administration of these drugs

with SPORANOX[®] is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and PRECAUTIONS: Drug Interactions.)

Cardiac Disease: SPORANOX[®] Oral Solution should not be used in patients with evidence of ventricular dysfunction unless the benefit clearly outweighs the risk. For patients with risk factors for congestive heart failure, physicians should carefully review the risks and benefits of SPORANOX[®] therapy. These risk factors include cardiac disease such as ischemic and valvular disease; significant pulmonary disease such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of CHF, should be treated with caution, and should be monitored for signs and symptoms of CHF during treatment. If signs or symptoms of CHF appear during administration of SPORANOX[®] Oral Solution, monitor carefully and consider other treatment alternatives which may include discontinuation of SPORANOX[®] Oral Solution administration.

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of SPORANOX[®] Injection (intravenous infusion), transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later.

Cases of CHF, peripheral edema, and pulmonary edema have been reported in the post-marketing period among patients being treated for onychomycosis and/or systemic fungal infections. (See CLINICAL PHARMACOLOGY: Special Populations, PRECAUTIONS: Drug Interactions, and ADVERSE REACTIONS: Post-marketing Experience for more information.)

PRECAUTIONS

General: Hepatic enzyme test values should be monitored in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications. Hepatic enzyme test values should be monitored periodically in all patients receiving continuous treatment for more than 1 month, or at any time a patient develops signs or symptoms suggestive of liver dysfunction.

Information for Patients:

- Only SPORANOX® Oral Solution has been demonstrated effective for oral and/or esophageal candidiasis. SPORANOX® Oral Solution contains the excipient hydroxypropyl- β -cyclodextrin which produced pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings is unknown. (See Carcinogenesis, Mutagenesis, and Impairment of Fertility.)
- Taking SPORANOX® Oral Solution under fasted conditions improves the systemic availability of itraconazole. Instruct patients to take SPORANOX® Oral Solution without food, if possible.
- SPORANOX® Oral Solution should not be used interchangeably with SPORANOX® Capsules.
- Instruct patients about the signs and symptoms of congestive heart failure, and if these signs or symptoms occur during SPORANOX® administration, they should discontinue SPORANOX® and contact their healthcare provider immediately.
- Instruct patients to report any signs and symptoms that may suggest liver dysfunction so that the appropriate laboratory testing can be done. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine or pale stools.
- Instruct patients to contact their physician before taking any concomitant medications with itraconazole to ensure there are no potential drug interactions.

Drug Interactions: Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of CYP3A4. Therefore, the following drug interactions may occur (See Table 1 below and the following drug class subheadings that follow):

1. SPORANOX® may decrease the elimination of drugs metabolized by CYP3A4, resulting in increased plasma concentrations of these drugs when they are administered with SPORANOX®. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. Whenever possible, plasma concentrations of these drugs should be monitored, and dosage adjustments made after

concomitant SPORANOX[®] therapy is initiated. When appropriate, clinical monitoring for signs or symptoms of increased or prolonged pharmacologic effects is advised. Upon discontinuation, depending on the dose and duration of treatment, itraconazole plasma concentrations decline gradually (especially in patients with hepatic cirrhosis or in those receiving CYP3A4 inhibitors). This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole.

2. Inducers of CYP3A4 may decrease the plasma concentrations of itraconazole. SPORANOX[®] may not be effective in patients concomitantly taking SPORANOX[®] and one of these drugs. Therefore, administration of these drugs with SPORANOX[®] is not recommended.
3. Other inhibitors of CYP3A4 may increase the plasma concentrations of itraconazole. Patients who must take SPORANOX[®] concomitantly with one of these drugs should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of SPORANOX[®].

Table 1. Selected Drugs that are predicted to alter the plasma concentration of itraconazole or have their plasma concentration altered by SPORANOX®¹

Drug plasma concentration increased by itraconazole	
Antiarrhythmics	digoxin, dofetilide ² , quinidine ²
Anticoagulants	warfarin
Anticonvulsants	carbamazepine
Antimycobacterials	rifabutin
Antineoplastics	busulfan, docetaxel, vinca alkaloids
Antipsychotics	pimozide ²
Benzodiazepines	alprazolam, diazepam, midazolam, ^{2,3} triazolam ²
Calcium Channel Blockers	dihydropyridines, verapamil
Gastrointestinal Motility Agents	cisapride ²
HMG CoA-Reductase Inhibitors	atorvastatin, cerivastatin, lovastatin, ² simvastatin ²
Immunosuppressants	cyclosporine, tacrolimus, sirolimus
Oral Hypoglycemics	oral hypoglycemics
Protease Inhibitors	indinavir, ritonavir, saquinavir
Other	alfentanil, buspirone, methylprednisolone, trimetrexate

Decrease plasma concentration of itraconazole	
Anticonvulsants	carbamazepine, phenobarbital, phenytoin
Antimycobacterials	isoniazid, rifabutin, rifampin
Gastric Acid Suppressors/Neutralizers	antacids, H ₂ -receptor antagonists, proton pump inhibitors
Reverse Transcriptase Inhibitors	nevirapine

Increase plasma concentration of itraconazole	
Macrolide Antibiotics	clarithromycin, erythromycin
Protease Inhibitors	indinavir, ritonavir

¹This list is not all-inclusive.²Contraindicated with SPORANOX® based on clinical and/or pharmacokinetics studies. (See WARNINGS and below.)³For information on parenterally administered midazolam, see the Benzodiazepine paragraph below.

Antiarrhythmics: The class IA antiarrhythmic quinidine and class III antiarrhythmic dofetilide are known to prolong the QT interval. Coadministration of quinidine or dofetilide with SPORANOX® may increase plasma concentrations of quinidine or dofetilide which could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX® and quinidine or dofetilide is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

Concomitant administration of digoxin and SPORANOX® has led to increased plasma concentrations of digoxin.

Anticoagulants: SPORANOX® enhances the anticoagulant effect of coumarin-like drugs, such as warfarin.

Anticonvulsants: Reduced plasma concentrations of itraconazole were reported when SPORANOX® was administered concomitantly with phenytoin. Carbamazepine, phenobarbital, and phenytoin are all inducers of CYP3A4. Although interactions with carbamazepine and phenobarbital have not been studied, concomitant administration of SPORANOX® and these drugs would be expected to result in decreased plasma concentrations of itraconazole. In addition, in vivo studies have demonstrated an increase in plasma carbamazepine concentrations in subjects concomitantly receiving ketoconazole. Although there are no data regarding the effect of itraconazole on carbamazepine metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX® and carbamazepine may inhibit the metabolism of carbamazepine.

Antimycobacterials: Drug interaction studies have demonstrated that plasma concentrations of azole antifungal agents and their metabolites, including itraconazole and hydroxyitraconazole, were significantly decreased when these agents were given concomitantly with rifabutin or rifampin. In vivo data suggest that rifabutin is metabolized in part by CYP3A4. SPORANOX® may inhibit the metabolism of rifabutin. Although no formal study data are available for isoniazid, similar effects should be anticipated. Therefore, the efficacy of SPORANOX® could be substantially reduced if given concomitantly with one of these agents. Coadministration is not recommended.

Antineoplastics: SPORANOX® may inhibit the metabolism of busulfan, docetaxel, and vinca alkaloids.

Antipsychotics: Pimozide is known to prolong the QT interval and is partially metabolized by CYP3A4. Coadministration of pimozide with SPORANOX® could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX® and pimozide is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

Benzodiazepines: Concomitant administration of SPORANOX® and alprazolam, diazepam, oral midazolam, or triazolam could lead to increased plasma concentrations of these benzodiazepines. Increased plasma concentrations could potentiate and prolong hypnotic and sedative effects. Concomitant administration of SPORANOX® and oral midazolam or triazolam is contraindicated. (See CONTRAINDICATIONS and WARNINGS.) If midazolam is administered parenterally, special precaution and patient monitoring is required since the sedative effect may be prolonged.

Calcium Channel Blockers: Edema has been reported in patients concomitantly receiving SPORANOX® and dihydropyridine calcium channel blockers. Appropriate dosage adjustment may be necessary.

Calcium channel blockers can have a negative inotropic effect which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers such as dihydropyridines (e.g., nifedipine and felodipine) and verapamil. Therefore, caution should be used when co-administering itraconazole and calcium channel blockers. (See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and ADVERSE REACTIONS: Post-marketing Experience for more information).

Gastric Acid Suppressors/Neutralizers: Reduced plasma concentrations of itraconazole were reported when SPORANOX® Capsules were administered concomitantly with H₂-receptor antagonists. Studies have shown that absorption of itraconazole is impaired when gastric acid production is decreased. Therefore, SPORANOX® should be administered with a cola beverage if the patient has achlorhydria or is taking H₂-receptor antagonists or other gastric acid suppressors. Antacids should be administered at least 1 hour before or 2 hours after administration of SPORANOX® Capsules. In a clinical study, when SPORANOX® Capsules were administered with omeprazole (a proton pump inhibitor), the bioavailability of itraconazole was significantly reduced. However, as itraconazole is already dissolved in SPORANOX® Oral Solution, the effect of H₂ antagonists

is expected to be substantially less than with the capsules. Nevertheless, caution is advised when the two drugs are coadministered.

Gastrointestinal Motility Agents: Coadministration of SPORANOX® with cisapride can elevate plasma cisapride concentrations which could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX® with cisapride is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

HMG CoA-Reductase Inhibitors: Human pharmacokinetic data suggest that SPORANOX® inhibits the metabolism of atorvastatin, cerivastatin, lovastatin, and simvastatin, which may increase the risk of skeletal muscle toxicity, including rhabdomyolysis. Concomitant administration of SPORANOX® with HMG CoA-reductase inhibitors, such as lovastatin and simvastatin, is contraindicated. (See CONTRAINDICATIONS, and WARNINGS.)

Immunosuppressants: Concomitant administration of SPORANOX® and cyclosporine or tacrolimus has led to increased plasma concentrations of these immunosuppressants. Concomitant administration of SPORANOX® and sirolimus could increase plasma concentrations of sirolimus.

Macrolide Antibiotics: Erythromycin and clarithromycin are known inhibitors of CYP3A4 (See Table 1) and may increase plasma concentrations of itraconazole. In a small pharmacokinetic study involving HIV infected patients, clarithromycin was shown to increase plasma concentrations of itraconazole. Similarly, following administration of 1 gram of erythromycin ethyl succinate and 200 mg itraconazole as single doses, the mean C_{max} and $AUC_{0-\infty}$ of itraconazole increased by 44% (90% CI: 119-175%) and 36% (90% CI: 108-171%), respectively.

Oral Hypoglycemic Agents: Severe hypoglycemia has been reported in patients concomitantly receiving azole antifungal agents and oral hypoglycemic agents. Blood glucose concentrations should be carefully monitored when SPORANOX® and oral hypoglycemic agents are coadministered.

Polyenes: Prior treatment with itraconazole, like other azoles, may reduce or inhibit the activity of polyenes such as amphotericin B. However, the clinical significance of this drug effect has not been clearly defined.

Protease Inhibitors: Concomitant administration of SPORANOX® and protease inhibitors metabolized by CYP3A4, such as indinavir, ritonavir, and saquinavir, may increase plasma concentrations of these protease inhibitors. In addition, concomitant administration of SPORANOX® and indinavir and ritonavir (but not saquinavir) may increase plasma concentrations of itraconazole. Caution is advised when SPORANOX® and protease inhibitors must be given concomitantly.

Reverse Transcriptase Inhibitors: Nevirapine is an inducer of CYP3A4. In vivo studies have shown that nevirapine induces the metabolism of ketoconazole, significantly reducing the bioavailability of ketoconazole. Studies involving nevirapine and itraconazole have not been conducted. However, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX® and nevirapine is not recommended. In a clinical study, when 8 HIV-infected subjects were treated concomitantly with SPORANOX® Capsules 100 mg twice daily and the nucleoside reverse transcriptase inhibitor zidovudine 8 ± 0.4 mg/kg/day, the pharmacokinetics of zidovudine were not affected. Other nucleoside reverse transcriptase inhibitors have not been studied.

Other:

- In vitro data suggest that alfentanil is metabolized by CYP3A4. Administration with SPORANOX® may increase plasma concentrations of alfentanil.
- Human pharmacokinetic data suggest that concomitant administration of SPORANOX® and buspirone results in significant increases in plasma concentrations of buspirone.
- SPORANOX® may inhibit the metabolism of methylprednisolone.
- In vitro data suggest that trimetrexate is extensively metabolized by CYP3A4. In vitro animal models have demonstrated that ketoconazole potently inhibits the metabolism of trimetrexate. Although there are no data regarding the effect of itraconazole on trimetrexate metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX® and trimetrexate may inhibit the metabolism of trimetrexate.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels up to 80 mg/kg/day (approximately 10x the maximum recommended human dose [MRHD]). Male rats treated with 25 mg/kg/day (3.1x MRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolemia, which is a response of rats, but not dogs or humans, to chronic itraconazole administration. Female rats treated with 50 mg/kg/day (6.25x MRHD) had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.

Hydroxypropyl- β -cyclodextrin (HP- β -CD), the solubilizing excipient used in SPORANOX® Oral Solution, was found to produce pancreatic exocrine hyperplasia and neoplasia when administered orally to rats at doses of 500, 2000 or 5000 mg/kg/day for 25 months. Adenocarcinomas of the exocrine pancreas produced in the treated animals were not seen in the untreated group and are not reported in the historical controls. Development of these tumors may be related to a mitogenic action of cholecystokinin. This finding was not observed in the mouse carcinogenicity study at doses of 500, 2000 or 5000 mg/kg/day for 22-23 months; however, the clinical relevance of these findings is unknown. Based on body surface area comparisons, the exposure to humans of HP- β -CD at the recommended clinical dose of SPORANOX® Oral Solution, is approximately equivalent to 1.7 times the exposure at the lowest dose in the rat study.

Itraconazole produced no mutagenic effects when assayed in a DNA repair test (unscheduled DNA synthesis) in primary rat hepatocytes, in Ames tests with *Salmonella typhimurium* (6 strains) and *Escherichia coli*, in the mouse lymphoma gene mutation tests, in a sex-linked recessive lethal mutation (*Drosophila melanogaster*) test, in chromosome aberration tests in human lymphocytes, in a cell transformation test with C3H/10T½ C18 mouse embryo fibroblasts cells, in a dominant lethal mutation test in male and female mice, and in micronucleus tests in mice and rats.

Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels of up to 40 mg/kg/day (5x MRHD), even though parental toxicity was present at this dosage level. More severe signs of parental toxicity, including death, were present in the next higher dosage level, 160 mg/kg/day (20x MRHD).

Pregnancy: Teratogenic Effects. Pregnancy Category C: Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day (5-20x MRHD), and in mice at dosage levels of approximately 80 mg/kg/day (10x MRHD). In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.

There are no studies in pregnant women. SPORANOX® should be used in pregnancy only if the benefit outweighs the potential risk.

Nursing Mothers: Itraconazole is excreted in human milk; therefore, the expected benefits of SPORANOX® therapy for the mother should be weighed against the potential risk from exposure of itraconazole to the infant. The U.S. Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breast-feed to avoid potential transmission of HIV to uninfected infants.

Pediatric Use: The efficacy and safety of SPORANOX® have not been established in pediatric patients. A pharmacokinetic study was conducted with SPORANOX® Oral Solution in 26 pediatric patients, ages 6 months to 12 years, requiring systemic antifungal treatment. Itraconazole was dosed at 5 mg/kg once daily for two weeks and no serious unexpected adverse events were reported. (See CLINICAL PHARMACOLOGY.)

The long-term effects of itraconazole on bone growth in children are unknown. In three toxicology studies using rats, itraconazole induced bone defects at dosage levels as low as 20 mg/kg/day (2.5x MRHD). The induced defects included reduced bone plate activity, thinning of the zona compacta of the large bones, and increased bone fragility. At a dosage level of 80 mg/kg/day (10x MRHD) over 1 year or 160 mg/kg/day (20x MRHD) for 6 months, itraconazole induced small tooth pulp with hypocellular appearance in some rats. No such bone toxicity has been reported in adult patients.

ADVERSE REACTIONS

SPORANOX[®] has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, the risks and benefits of continued SPORANOX[®] use should be reassessed. (See WARNINGS: Hepatic Effects and PRECAUTIONS: Information for Patients.)

Adverse Events Reported in Empiric Therapy In Febrile Neutropenic (ETFN) Patients

Adverse events considered at least possibly drug related in a clinical trial of empiric therapy in 384 febrile, neutropenic patients (192 treated with SPORANOX[®] and 192 with amphotericin B) with suspected fungal infections are listed in Table 2 below. Patients received a regimen of SPORANOX[®] Injection followed by SPORANOX[®] Oral Solution. The dose of SPORANOX[®] Injection was 200 mg twice daily for the first two days followed by a single daily dose of 200 mg for the remainder of the intravenous treatment period. The majority of patients received between 7 and 14 days of SPORANOX[®] Injection. The dose of SPORANOX[®] Oral Solution was 200 mg (20 mL) b.i.d. for the remainder of therapy.

Table 2: Summary of possibly or definitely drug-related adverse events reported in $\geq 2\%$ of subjects (Empiric Therapy Trial in Febrile Neutropenic Patients)		
Adverse Event	SPORANOX[®] (N=192) %	Amphotericin B (N=192) %
Gastrointestinal system disorders		
Nausea	11	15
Diarrhea	10	9
Vomiting	7	10
Abdominal pain	3	3
Metabolic and nutritional disorders		
Hypokalemia	9	28
Serum creatinine increased	3	25
LDH increased	2	0
Alkaline phosphatase increased	2	2
Hypomagnesemia	2	4
Blood urea nitrogen increased	1	6
Fluid overload	1	3
Hypocalcemia	1	2
Liver and biliary system disorders		
Bilirubinemia	6	3
Hepatic function abnormal	3	2
SGPT/ALT increased	3	1
Jaundice	2	1
SGOT/AST increased	2	1
Skin and appendage disorders		
Rash	5	3
Sweating increased	2	1
CNS and peripheral nervous system		
Headache	2	2
Body as a whole		
Edema	2	2
Rigors	1	34
Fever	0	7
Respiratory system disorder		
Dyspnea	1	3
Urinary system disorder		
Renal function abnormal	1	12
Cardiovascular disorders, general		
Hypotension	1	3
Hypertension	0	2
Heart rate and rhythm disorders		
Tachycardia	1	3

The following additional adverse events considered at least possibly related occurred in between 1 and 2% of patients who received SPORANOX[®] Injection and Oral Solution: constipation, hypophosphatemia, gamma-GT increased, erythematous rash, pruritus, dizziness, tremor, and pulmonary infiltration.

Adverse Events Reported in Oropharyngeal or Esophageal Candidiasis Trials

U.S. adverse experience data are derived from 350 immunocompromised patients (332 HIV seropositive/AIDS) treated for oropharyngeal or esophageal candidiasis. Table 3 below lists adverse events reported by at least 2% of patients treated with SPORANOX[®] Oral Solution in U.S. clinical trials. Data on patients receiving comparator agents in these trials are included for comparison.

Table 3: Summary of Adverse Events Reported by >2% of Sporanox® Treated Patients in U.S. Clinical Trials (Total)

Body System/ Adverse Event	Itraconazole		Fluconazole (n = 125**) %	Clotrimazole (n = 81***) %
	Total (n = 350*) %	All controlled studies (n = 272) %		
Gastrointestinal disorders				
Nausea	11	10	11	5
Diarrhea	11	10	10	4
Vomiting	7	6	8	1
Abdominal pain	6	4	7	7
Constipation	2	2	1	0
Body as a whole				
Fever	7	6	8	5
Chest pain	3	3	2	0
Pain	2	2	4	0
Fatigue	2	1	2	0
Respiratory disorders				
Coughing	4	4	10	0
Dyspnea	2	3	5	1
Pneumonia	2	2	0	0
Sinusitis	2	2	4	0
Sputum increased	2	3	3	1
Skin and appendages disorders				
Rash	4	5	4	6
Increased sweating	3	4	6	1
Skin disorder, unspecified	2	2	2	1
Central/peripheral nervous system				
Headache	4	4	6	6
Dizziness	2	2	4	1
Resistance mechanism disorders				
Pneumocystis carinii Infection	2	2	2	0
Psychiatric disorders				
Depression	2	1	0	1

*Of the 350 patients, 209 were treated for oropharyngeal candidiasis in controlled studies, 63 were treated for esophageal candidiasis in controlled studies and 78 were treated for oropharyngeal candidiasis in an open study.

**Of the 125 patients, 62 were treated for oropharyngeal candidiasis and 63 were treated for esophageal candidiasis.

***All 81 patients were treated for oropharyngeal candidiasis.

Adverse events reported by less than 2% of patients in U.S. clinical trials with SPORANOX® included: adrenal insufficiency, asthenia, back pain, dehydration, dyspepsia, dysphagia, flatulence, gynecomastia, hematuria, hemorrhoids, hot flushes, implantation complication, infection unspecified, injury, insomnia, male breast pain, myalgia, pharyngitis, pruritus, rhinitis, rigors, stomatitis ulcerative, taste perversion, tinnitus, upper respiratory tract infection, vision abnormal, and weight decrease. Edema, hypokalemia and menstrual disorders have been reported in clinical trials with itraconazole capsules.

Post-marketing Experience

In worldwide post-marketing experience with SPORANOX® Capsules in treatment of onychomycosis and/or systemic fungal infections, peripheral edema, allergic reactions, including rash, pruritus, urticaria, angioedema, and, in rare instances, anaphylaxis and Stevens-Johnson syndrome, have been reported. Post-marketing experiences have also included reports of elevated liver enzymes and rarely liver failure. Rare cases of congestive heart failure and pulmonary edema have been reported. Rare cases of alopecia, hypertriglyceridemia, menstrual disorders, and neutropenia, and isolated cases of neuropathy have also been reported, although the causal association with SPORANOX® is uncertain. (See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.)

OVERDOSAGE

Itraconazole is not removed by dialysis. In the event of accidental overdosage, supportive measures, including gastric lavage with sodium bicarbonate, should be employed.

There are limited data on the outcomes of patients ingesting high doses of itraconazole. In patients taking either 1000 mg of SPORANOX® (itraconazole) Oral Solution or up to 3000 mg of SPORANOX® Capsules, the adverse event profile was similar to that observed at recommended doses.

DOSAGE AND ADMINISTRATION

Empiric Therapy in Febrile, Neutropenic Patients with Suspected Fungal Infections (ETFN): The recommended dose of SPORANOX® Injection is 200 mg BID for four doses, followed by 200 mg once daily for up to 14 days. Each intravenous dose should be infused

over 1 hour. Treatment should be continued with SPORANOX® Oral Solution 200 mg (20 mL) BID until resolution of clinically significant neutropenia. The safety and efficacy of SPORANOX® use exceeding 28 days in ETFN is not known.

SPORANOX® Oral Solution is a different preparation than SPORANOX® Capsules and should not be used interchangeably.

Treatment of Oropharyngeal and Esophageal Candidiasis:

The solution should be vigorously swished in the mouth (10 mL at a time) for several seconds and swallowed.

The recommended dosage of SPORANOX® (itraconazole) Oral Solution for oropharyngeal candidiasis is 200 mg (20 mL) daily for 1 to 2 weeks. Clinical signs and symptoms of oropharyngeal candidiasis generally resolve within several days.

For patients with oropharyngeal candidiasis unresponsive/refractory to treatment with fluconazole tablets, the recommended dose is 100 mg (10 mL) b.i.d. For patients responding to therapy, clinical response will be seen in 2 to 4 weeks. Patients may be expected to relapse shortly after discontinuing therapy. Limited data on the safety of long-term use (>6 months) of SPORANOX® Oral Solution are available at this time.

The recommended dosage of SPORANOX® Oral Solution for esophageal candidiasis is 100 mg (10 mL) daily for a minimum treatment of three weeks. Treatment should continue for 2 weeks following resolution of symptoms. Doses up to 200 mg (20 mL) per day may be used based on medical judgement of the patient's response to therapy.

SPORANOX® Oral Solution and SPORANOX® Capsules should not be used interchangeably. Patients should be instructed to take SPORANOX® Oral Solution without food, if possible. Only SPORANOX® Oral Solution has been demonstrated effective for oral and/or esophageal candidiasis.

HOW SUPPLIED

SPORANOX® (itraconazole) Oral Solution is available in 150 mL amber glass bottles (NDC 50458-295-15) containing 10 mg of itraconazole per mL.

Store at or below 25°C (77°F). Do not freeze.

Keep out of reach of children.

U.S. Patent No. 4,267,179; 5,707,975; 4,727,064

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Manufactured by:

Janssen Pharmaceutica N.V.

Beerse, Belgium

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ORTHO BIOTECH

SPORANOX[®]
(ITRACONAZOLE)
INJECTION

Congestive Heart Failure: When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen. If signs or symptoms of congestive heart failure occur during administration of SPORANOX[®] (itraconazole) Injection, continued SPORANOX[®] use should be reassessed. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Post-marketing Experience for more information.)

Drug Interactions: Coadministration of cisapride, pimozide, ~~or~~ quinidine, or dofetilide with SPORANOX[®] (itraconazole) Capsules, Injection or Oral Solution is contraindicated. SPORANOX[®], a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, or quinidine, concomitantly with SPORANOX[®] and/or other CYP3A4 inhibitors. See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.

DESCRIPTION

For intravenous infusion (NOT FOR IV BOLUS INJECTION)

SPORANOX[®] is the brand name for itraconazole, a synthetic triazole antifungal agent. Itraconazole is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs), each possessing three chiral centers. It may be represented by the following structural formula and nomenclature:

(insert structure)

(±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[(2R*,4S*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]- Δ^2 -1,2,4-triazolin-5-one mixture with (±)-1-[(R*)-sec-butyl]-4-[p-[4-[p-[(2S*,4R*)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]- Δ^2 -1,2,4-triazolin-5-one

or

(±)-1-[(RS)-sec-butyl]-4-[p-[4-[p-[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]- Δ^2 -1,2,4-triazolin-5-one.

Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.64. It is a white to slightly yellowish powder. It is insoluble in water, very slightly soluble in alcohols, and freely soluble in dichloromethane. It has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions) and a log (n-octanol/water) partition coefficient of 5.66 at pH 8.1.

SPORANOX® (itraconazole) Injection is a sterile pyrogen-free clear, colorless to slightly yellow solution for intravenous infusion. Each mL contains 10 mg of itraconazole, solubilized by hydroxypropyl- β -cyclodextrin (400 mg) as a molecular inclusion complex, with 3.8 μ L hydrochloric acid, 25 μ L propylene glycol, and sodium hydroxide for pH adjustment to 4.5, in water for injection. SPORANOX® Injection is packaged in 25 mL colorless glass ampules, containing 250 mg of itraconazole, contents of which are diluted in 50 mL 0.9% Sodium Chloride Injection, USP (Normal Saline) prior to infusion. When properly administered, contents of one ampule will supply 200 mg of itraconazole.

CLINICAL PHARMACOLOGY

Pharmacokinetics and Metabolism: NOTE: The plasma concentrations reported below were measured by high-performance liquid chromatography (HPLC) specific for itraconazole. When itraconazole in plasma is measured by a bioassay, values reported may be higher than those obtained by HPLC due to the presence of the bioactive metabolite, hydroxyitraconazole. (See MICROBIOLOGY.)

The pharmacokinetics of SPORANOX® (itraconazole) Injection (200 mg b.i.d. for two days, then 200 mg q.d. for five days) followed by oral dosing of SPORANOX® Capsules were studied in patients with advanced HIV infection. Steady-state plasma concentrations were reached after the fourth dose for itraconazole and by the seventh dose for

hydroxyitraconazole. Steady-state plasma concentrations were maintained by administration of SPORANOX® Capsules, 200 mg b.i.d. Pharmacokinetic parameters for itraconazole and hydroxyitraconazole are presented in the table below:

Parameter	Injection Day 7 n=29		Capsule, 200 mg b.i.d. Day 36 n=12	
	itraconazole	hydroxyitraconazole	itraconazole	hydroxyitraconazole
C_{max} (ng/mL)	2856 ± 866*	1906 ± 612	2010 ± 1420	2614 ± 1703
T_{max} (hr)	1.08 ± 0.14	8.53 ± 6.36	3.92 ± 1.83	5.92 ± 6.14
AUC_{0-12h} (ng•h/mL)	--	--	18768 ± 13933	28516 ± 19149
AUC_{0-24h} (ng•h/mL)	30605 ± 8961	42445 ± 13282	--	--

*mean ± standard deviation

The estimated mean ±SD half-life at steady-state of itraconazole after intravenous infusion was 35.4 ± 29.4 hours. In previous studies, the mean elimination half-life for itraconazole at steady-state after daily oral administration of 100 to 400 mg was 30–40 hours.

Approximately 93-101% of hydroxypropyl-β-cyclodextrin was excreted unchanged in the urine within 12 hours after dosing.

The plasma protein binding of itraconazole is 99.8% and that of hydroxyitraconazole is 99.5%. Following intravenous administration, the volume of distribution of itraconazole averaged 796 ± 185 L.

Itraconazole is metabolized predominately by the cytochrome P450 3A4 isoenzyme system (CYP3A4), resulting in the formation of several metabolites, including hydroxyitraconazole, the major metabolite. Results of a pharmacokinetics study suggest that itraconazole may undergo saturable metabolism with multiple dosing. Fecal excretion of the parent drug varies between 3-18% of the dose. Renal excretion of the parent drug is less than 0.03% of the dose. About 40% of the dose is excreted as inactive metabolites in the urine. No single excreted metabolite represents more than 5% of a dose. Itraconazole total plasma clearance averaged 381 ± 95 mL/min following intravenous administration. Approximately 80-90% of hydroxypropyl-β-cyclodextrin is eliminated through the kidneys. (See CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions for more information.)

Special Populations

Renal Insufficiency: Plasma concentrations of itraconazole in patients with mild to moderate renal insufficiency were comparable to those obtained in healthy subjects. The majority of the 8-gram dose of hydroxypropyl- β -cyclodextrin was eliminated in the urine during the 120-hour collection period in normal subjects and in patients with mild to severe renal insufficiency. Following a single intravenous dose of 200 mg to subjects with severe renal impairment (creatinine clearance ≤ 19 mL/minute), clearance of hydroxypropyl- β -cyclodextrin was reduced six-fold compared with subjects with normal renal function. SPORANOX[®] Injection should not be used in patients with creatinine clearance < 30 mL/min.

Hepatic Insufficiency: Patients with impaired hepatic function should be carefully monitored when taking itraconazole. The prolonged elimination half-life of itraconazole observed in a clinical trial with itraconazole capsules in cirrhotic patients should be considered when deciding to initiate therapy with other medications metabolized by CYP3A4. (See BOX WARNING, CONTRAINDICATIONS, and PRECAUTIONS: Drug Interactions.)

Decreased Cardiac Contractility: When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of SPORANOX[®] Injection (intravenous infusion), transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later. If signs or symptoms of congestive heart failure appear during administration of SPORANOX[®] Injection, monitor carefully and consider other treatment alternatives which may include discontinuation of SPORANOX[®] Injection administration. (See WARNINGS, PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Post-marketing Experience for more information.)

MICROBIOLOGY

Mechanism of Action: In vitro studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

Activity In Vitro and In Vivo: Itraconazole exhibits in vitro activity against *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Histoplasma duboisii*, *Aspergillus flavus*,

Aspergillus fumigatus, *Candida albicans*, and *Cryptococcus neoformans*. Itraconazole also exhibits varying in vitro activity against *Sporothrix schenckii*, *Trichophyton* species, *Candida krusei*, and other *Candida* species. The bioactive metabolite, hydroxyitraconazole, has not been evaluated against *Histoplasma capsulatum* and *Blastomyces dermatitidis*. Correlation between minimum inhibitory concentration (MIC) results in vitro and clinical outcome has yet to be established for azole antifungal agents.

Itraconazole administered orally was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Fungistatic activity has been demonstrated against disseminated fungal infections caused by *Blastomyces dermatitidis*, *Histoplasma duboisii*, *Aspergillus fumigatus*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*.

Itraconazole administered at 2.5 mg/kg and 5 mg/kg via the oral and parenteral routes increased survival rates and sterilized organ systems in normal and immunosuppressed guinea pigs with disseminated *Aspergillus fumigatus* infections. Oral itraconazole administered daily at 40 mg/kg and 80 mg/kg increased survival rates in normal rabbits with disseminated disease and in immunosuppressed rats with pulmonary *Aspergillus fumigatus* infection, respectively. Itraconazole has demonstrated antifungal activity in a variety of animal models infected with *Candida albicans* and other *Candida* species.

Resistance: Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated in vitro and from patients receiving prolonged therapy.

Several in vitro studies have reported that some fungal clinical isolates, including *Candida* species, with reduced susceptibility to one azole antifungal agent may also be less susceptible to other azole derivatives. The finding of cross-resistance is dependent on a number of factors, including the species evaluated, its clinical history, the particular azole compounds compared, and the type of susceptibility test that is performed. The relevance of these in vitro susceptibility data to clinical outcome remains to be elucidated.

Studies (both in vitro and in vivo) suggest that the activity of amphotericin B may be suppressed by prior azole antifungal therapy. As with other azoles, itraconazole inhibits the ¹⁴C-demethylation step in the synthesis of ergosterol, a cell wall component of fungi. Ergosterol is the active site for amphotericin B. In one study the antifungal activity of amphotericin B against *Aspergillus fumigatus* infections in mice was inhibited by

ketoconazole therapy. The clinical significance of test results obtained in this study is unknown.

CLINICAL STUDIES

Empiric Therapy in Febrile Neutropenic Patients: An open randomized trial compared the efficacy and safety of itraconazole (intravenous followed by oral solution) with amphotericin B for empiric therapy in 384 febrile, neutropenic patients with hematologic malignancies who had suspected fungal infections. Patients received either itraconazole (injection, 200 mg BID for 2 days followed by 200 mg once daily for up to 14 days, followed by oral solution, 200 mg BID) or amphotericin B (total daily dose of 0.7-1.0 mg/kg body weight). The longest treatment duration was 28 days. An outcome assignment of "success" required (a) patient survival with resolution of fever and neutropenia within 28 days of treatment, (b) absence of emergent fungal infections, (c) no discontinuation of therapy due to toxicity or lack of efficacy, and (d) treatment for three or more days. The success rate using an intent-to-treat analysis was 47% for the itraconazole group and 38% for the amphotericin B arm.

**Overview of Efficacy
(Intent-to-Treat Population)**

Efficacy Parameters	SPORANOX N=179 (%)	Amphotericin B N=181 (%)
Success	84 (47%)	68 (38%)
Unevaluable*	24 (13%)	44 (24%)
Failure	71 (40%)	69 (38%)
Reason for Failure		
Intolerance after > 3 days of antifungal medication	12	37
Persistent fever	20	7
Change in antifungal medication due to fever	13	1
Emergent fungal infection	10	9
Documented bacterial or viral infection	7	8
Insufficient response	6	5
Deterioration of signs and symptoms	2	0
Death after > 3 days antifungal medication	1	2
Resolution of fever	131 (73%)	127 (70%)
Survival	161 (90%)	156 (86%)

* Treatment duration ≤ 3 days (including patients who died within 3 days, withdrew because of adverse events or were deemed ineligible due to a confirmed pre-treatment infection.)

INDICATIONS AND USAGE

SPORANOX® (itraconazole) Injection/Oral Solution is indicated for empiric therapy of febrile neutropenic patients with suspected fungal infections. (NOTE: In a comparative trial, the overall response rate for itraconazole-treated subjects was higher than for amphotericin B-treated subjects. However, compared to amphotericin B-treated subjects, a larger number of itraconazole-treated subjects discontinued treatment due to persistent fever and a change in antifungal medication due to fever. Whereas, a larger number of amphotericin B-treated subjects discontinued due to drug intolerance. (See CLINICAL STUDIES section.)

SPORANOX® (itraconazole) Injection is also indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

1. Blastomycosis, pulmonary and extrapulmonary;
2. Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis; and
3. Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy.

Specimens for fungal cultures and other relevant laboratory studies (wet mount, histopathology, serology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

(See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and ADVERSE REACTIONS: Post-marketing Experience for more information).

CONTRAINDICATIONS

Drug Interactions: Concomitant administration of SPORANOX® (itraconazole) Capsules, Injection, or Oral Solution and certain drugs metabolized by the cytochrome P450 3A4 isoenzyme system (CYP3A4) may result in increased plasma concentrations of those drugs, leading to potentially serious and/or life-threatening adverse events. Cisapride, oral midazolam, pimozide, quinidine, dofetilide and triazolam are contraindicated with SPORANOX®. HMG CoA-reductase inhibitors metabolized by CYP3A4, such as lovastatin

and simvastatin, are also contraindicated with SPORANOX®. (See BOX WARNING, and PRECAUTIONS: Drug Interactions.)

SPORANOX® is contraindicated for patients who have shown hypersensitivity to itraconazole or its excipients. There is no information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used when prescribing SPORANOX® to patients with hypersensitivity to other azoles.

WARNINGS

SPORANOX® (itraconazole) Injection contains the excipient hydroxypropyl- β -cyclodextrin which produced pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings is unknown. (See PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

Hepatic Effects: SPORANOX® has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, the risks and benefits of continued SPORANOX® use should be reassessed. (See PRECAUTIONS: Information for Patients and ADVERSE REACTIONS.)

Cardiac Dysrhythmias: Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using cisapride, pimozide or quinidine concomitantly with SPORANOX® and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with SPORANOX® is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and PRECAUTIONS: Drug Interactions.)

Cardiac Disease: SPORANOX® Injection should not be used in patients with evidence of ventricular dysfunction unless the benefit clearly outweighs the risk. For patients with risk factors for congestive heart failure, physicians should carefully review the risks and benefits of SPORANOX® therapy. These risk factors include cardiac disease such as ischemic and valvular disease; significant pulmonary disease such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of CHF, should be treated with caution, and should be monitored for signs and symptoms of CHF during treatment. If signs or symptoms of CHF

appear during administration of SPORANOX® Injection, monitor carefully and consider other treatment alternatives which may include discontinuation of SPORANOX® Injection administration.

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of SPORANOX® Injection (intravenous infusion), transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later.

Cases of CHF, peripheral edema, and pulmonary edema have been reported in the post-marketing period among patients being treated for onychomycosis and/or systemic fungal infections. (See CLINICAL PHARMACOLOGY: Special Populations, PRECAUTIONS: Drug Interactions, and ADVERSE REACTIONS: Post-marketing Experience for more information.)

PRECAUTIONS

General: Hepatic enzyme test values should be monitored in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications. Hepatic enzyme test values should be monitored periodically in all patients receiving continuous treatment for more than 1 month, or at any time a patient develops signs or symptoms suggestive of liver dysfunction.

As severe renal impairment prolongs the elimination rate of hydroxypropyl- β -cyclodextrin, SPORANOX® (itraconazole) Injection should not be used in patients with severe renal dysfunction (creatinine clearance < 30 mL/min). (See CLINICAL PHARMACOLOGY: Special Populations.)

Information for Patients: SPORANOX® Injection contains the excipient hydroxypropyl- β -cyclodextrin which produced pancreatic adenocarcinomas in a rat carcinogenicity study. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of these findings is unknown. (See PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility.)

Drug Interactions: Itraconazole and its major metabolite, hydroxyitraconazole, are inhibitors of CYP3A4. Therefore, the following drug interactions may occur (See Table 1 below and the following drug class subheadings that follow):

SPORANOX® may decrease the elimination of drugs metabolized by CYP3A4, resulting in increased plasma concentrations of these drugs when they are administered with SPORANOX®. These elevated plasma concentrations may increase or prolong both therapeutic and adverse effects of these drugs. Whenever possible, plasma concentrations of these drugs should be monitored, and dosage adjustments made after concomitant SPORANOX® therapy is initiated. When appropriate, clinical monitoring for signs or symptoms of increased or prolonged pharmacologic effects is advised. Upon discontinuation, depending on the dose and duration of treatment, itraconazole plasma concentrations decline gradually (especially in patients with hepatic cirrhosis or in those receiving CYP3A4 inhibitors). This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole.

Inducers of CYP3A4 may decrease the plasma concentrations of itraconazole. SPORANOX® may not be effective in patients concomitantly taking SPORANOX® and one of these drugs. Therefore, administration of these drugs with SPORANOX® is not recommended.

Other inhibitors of CYP3A4 may increase the plasma concentrations of itraconazole. Patients who must take SPORANOX® concomitantly with one of these drugs should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of SPORANOX®.

Table 1. Selected Drugs that are predicted to alter the plasma concentration of itraconazole or have their plasma concentration altered by SPORANOX®¹	
Drug plasma concentration increased by itraconazole	
Antiarrhythmics	digoxin, dofetilide ² , quinidine ²
Anticonvulsants	carbamazepine
Antimycobacterials	rifabutin
Antineoplastics	busulfan, docetaxel, vinca alkaloids
Antipsychotics	pimozide ²
Benzodiazepines	alprazolam, diazepam, midazolam, ^{2,3} triazolam ²
Calcium Channel Blockers	dihydropyridines, verapamil
Gastrointestinal Motility Agents	cisapride ²
HMG CoA-Reductase Inhibitors	atorvastatin, cerivastatin, lovastatin, ² simvastatin ²
Immunosuppressants	cyclosporine, tacrolimus, sirolimus
Oral Hypoglycemics	oral hypoglycemics
Protease Inhibitors	indinavir, ritonavir, saquinavir
Other	alfentanil, buspirone, methylprednisolone, trimetrexate, warfarin
Decrease plasma concentration of itraconazole	
Anticonvulsants	carbamazepine, phenobarbital, phenytoin
Antimycobacterials	isoniazid, rifabutin, rifampin
Reverse Transcriptase Inhibitors	nevirapine
Increase plasma concentration of itraconazole	
Macrolide Antibiotics	clarithromycin, erythromycin
Protease Inhibitors	indinavir, ritonavir

¹This list is not all-inclusive.

²Contraindicated with SPORANOX® based on clinical and/or pharmacokinetics studies. (See WARNINGS and below.)

³For information on parenterally administered midazolam, see the Benzodiazepine paragraph below.

Antiarrhythmics: The class IA antiarrhythmic quinidine and class III antiarrhythmic dofetilide are known to prolong the QT interval. Coadministration of quinidine or dofetilide with SPORANOX® may increase plasma concentrations of quinidine or dofetilide which could result in serious cardiovascular events. Therefore, concomitant administration of

SPORANOX[®] and quinidine or dofetilide is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

Concomitant administration of digoxin and SPORANOX[®] has led to increased plasma concentrations of digoxin.

Anticonvulsants: Reduced plasma concentrations of itraconazole were reported when SPORANOX[®] was administered concomitantly with phenytoin. Carbamazepine, phenobarbital, and phenytoin are all inducers of CYP3A4. Although interactions with carbamazepine and phenobarbital have not been studied, concomitant administration of SPORANOX[®] and these drugs would be expected to result in decreased plasma concentrations of itraconazole. In addition, in vivo studies have demonstrated an increase in plasma carbamazepine concentrations in subjects concomitantly receiving ketoconazole. Although there are no data regarding the effect of itraconazole on carbamazepine metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX[®] and carbamazepine may inhibit the metabolism of carbamazepine.

Antimycobacterials: Drug interaction studies have demonstrated that plasma concentrations of azole antifungal agents and their metabolites, including itraconazole and hydroxyitraconazole, were significantly decreased when these agents were given concomitantly with rifabutin or rifampin. In vivo data suggest that rifabutin is metabolized in part by CYP3A4. SPORANOX[®] may inhibit the metabolism of rifabutin. Although no formal study data are available for isoniazid, similar effects should be anticipated. Therefore, the efficacy of SPORANOX[®] could be substantially reduced if given concomitantly with one of these agents. Coadministration is not recommended.

Antineoplastics: SPORANOX[®] may inhibit the metabolism of busulfan, docetaxel, and vinca alkaloids.

Antipsychotics: Pimozide is known to prolong the QT interval and is partially metabolized by CYP3A4. Coadministration of pimozide with SPORANOX[®] could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX[®] and pimozide is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

Benzodiazepines: Concomitant administration of SPORANOX® and alprazolam, diazepam, oral midazolam, or triazolam could lead to increased plasma concentrations of these benzodiazepines. Increased plasma concentrations could potentiate and prolong hypnotic and sedative effects. Concomitant administration of SPORANOX® and oral midazolam or triazolam is contraindicated. (See CONTRAINDICATIONS and WARNINGS.) If midazolam is administered parenterally, special precaution and patient monitoring is required since the sedative effect may be prolonged.

Calcium Channel Blockers: Edema has been reported in patients concomitantly receiving SPORANOX® and dihydropyridine calcium channel blockers. Appropriate dosage adjustment may be necessary.

Calcium channel blockers can have a negative inotropic effect which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers such as dihydropyridines (e.g., nifedipine and felodipine) and verapamil. Therefore, caution should be used when co-administering itraconazole and calcium channel blockers. (See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and ADVERSE REACTIONS: Post-marketing Experience for more information).

Gastrointestinal Motility Agents: Coadministration of SPORANOX® with cisapride can elevate plasma cisapride concentrations which could result in serious cardiovascular events. Therefore, concomitant administration of SPORANOX® with cisapride is contraindicated. (See BOX WARNING, CONTRAINDICATIONS, and WARNINGS.)

HMG CoA-Reductase Inhibitors: Human pharmacokinetic data suggest that SPORANOX® inhibits the metabolism of atorvastatin, cerivastatin, lovastatin, and simvastatin, which may increase the risk of skeletal muscle toxicity, including rhabdomyolysis. Concomitant administration of SPORANOX® with HMG CoA-reductase inhibitors, such as lovastatin and simvastatin, is contraindicated. (See CONTRAINDICATIONS, and WARNINGS.)

Immunosuppressants: Concomitant administration of SPORANOX® and cyclosporine or tacrolimus has led to increased plasma concentrations of these immunosuppressants. Concomitant administration of SPORANOX® and sirolimus could increase plasma concentrations of sirolimus.

Macrolide Antibiotics: Erythromycin and clarithromycin are known inhibitors of CYP3A4 (See Table 1) and may increase plasma concentrations of itraconazole. In a small pharmacokinetic study involving HIV infected patients, clarithromycin was shown to increase plasma concentrations of itraconazole. Similarly, following administration of 1 gram of erythromycin ethyl succinate and 200 mg itraconazole as single doses, the mean C_{max} and $AUC_{0-\infty}$ of itraconazole increased by 44% (90% CI: 119-175%) and 36% (90% CI: 108-171%), respectively.

Oral Hypoglycemic Agents: Severe hypoglycemia has been reported in patients concomitantly receiving azole antifungal agents and oral hypoglycemic agents. Blood glucose concentrations should be carefully monitored when SPORANOX® and oral hypoglycemic agents are coadministered.

Polyenes: Prior treatment with itraconazole, like other azoles, may reduce or inhibit the activity of polyenes such as amphotericin B. However, the clinical significance of this drug effect has not been clearly defined.

Protease Inhibitors: Concomitant administration of SPORANOX® and protease inhibitors metabolized by CYP3A4, such as indinavir, ritonavir, and saquinavir, may increase plasma concentrations of these protease inhibitors. In addition, concomitant administration of SPORANOX® and indinavir and ritonavir (but not saquinavir) may increase plasma concentrations of itraconazole. Caution is advised when SPORANOX® and protease inhibitors must be given concomitantly.

Reverse Transcriptase Inhibitors: Nevirapine is an inducer of CYP3A4. In vivo studies have shown that nevirapine induces the metabolism of ketoconazole, significantly reducing the bioavailability of ketoconazole. Studies involving nevirapine and itraconazole have not been conducted. However, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX® and nevirapine is not recommended. In a clinical study, when 8 HIV-infected subjects were treated concomitantly with SPORANOX® Capsules 100 mg twice daily and the nucleoside reverse transcriptase inhibitor zidovudine 8 ± 0.4 mg/kg/day, the pharmacokinetics of zidovudine were not affected. Other nucleoside reverse transcriptase inhibitors have not been studied.

Other:

- In vitro data suggest that alfentanil is metabolized by CYP3A4. Administration with SPORANOX® may increase plasma concentrations of alfentanil.
- Human pharmacokinetic data suggest that concomitant administration of SPORANOX® and buspirone results in significant increases in plasma concentrations of buspirone.
- SPORANOX® may inhibit the metabolism of methylprednisolone.
- In vitro data suggest that trimetrexate is extensively metabolized by CYP3A4. In vitro animal models have demonstrated that ketoconazole potently inhibits the metabolism of trimetrexate. Although there are no data regarding the effect of itraconazole on trimetrexate metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX® and trimetrexate may inhibit the metabolism of trimetrexate.
- SPORANOX® enhances the anticoagulant effect of coumarin-like drugs, such as warfarin.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels up to 80 mg/kg/day (approximately 10x the maximum recommended human dose [MRHD]). Male rats treated with 25 mg/kg/day (3.1x MRHD) had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolemia, which is a response of rats, but not dogs or humans, to chronic itraconazole administration. Female rats treated with 50 mg/kg/day (6.25x MRHD) had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.

Hydroxypropyl- β -cyclodextrin (HP- β -CD), the solubilizing excipient used in SPORANOX® Injection and Oral Solution, was found to produce pancreatic exocrine hyperplasia and neoplasia when administered orally to rats at doses of 500, 2000 or 5000 mg/kg/day for 25 months. Adenocarcinomas of the exocrine pancreas produced in the treated animals were not seen in the untreated group and are not reported in the historical controls. Development of these tumors may be related to a mitogenic action of cholecystokinin. This finding was not observed in the mouse carcinogenicity study at doses of 500, 2000 or 5000 mg/kg/day for 22-23 months; however, the clinical relevance of these findings is unknown. Based on

body surface area comparisons, the exposure to humans of HP- β -CD at the recommended clinical dose of SPORANOX[®] Oral Solution, is approximately equivalent to 1.7 times the exposure at the lowest dose in the rat study. The relevance of the findings with orally administered HP- β -CD to potential carcinogenic effects for SPORANOX[®] Injection is uncertain.

Itraconazole produced no mutagenic effects when assayed in a DNA repair test (unscheduled DNA synthesis) in primary rat hepatocytes, in Ames tests with *Salmonella typhimurium* (6 strains) and *Escherichia coli*, in the mouse lymphoma gene mutation tests, in a sex-linked recessive lethal mutation (*Drosophila melanogaster*) test, in chromosome aberration tests in human lymphocytes, in a cell transformation test with C3H/10T $\frac{1}{2}$ 18 mouse embryo fibroblasts cells, in a dominant lethal mutation test in male and female mice, and in micronucleus tests in mice and rats.

Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels of up to 40 mg/kg/day (5x MRHD), even though parental toxicity was present at this dosage level. More severe signs of parental toxicity, including death, were present in the next higher dosage level, 160 mg/kg/day (20x MRHD).

Pregnancy: Teratogenic Effects. Pregnancy Category C: Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day (5-20x MRHD), and in mice at dosage levels of approximately 80 mg/kg/day (10x MRHD). In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and/or macroglossia.

There are no studies in pregnant women. SPORANOX[®] should be used for the treatment of systemic fungal infections in pregnancy only if the benefit outweighs the potential risk.

Nursing Mothers: Itraconazole is excreted in human milk; therefore, the expected benefits of SPORANOX[®] therapy for the mother should be weighed against the potential risk from exposure of itraconazole to the infant. The U.S. Public Health Service Centers for Disease Control and Prevention advises HIV-infected women not to breast-feed to avoid potential transmission of HIV to uninfected infants.

Pediatric Use: The efficacy and safety of SPORANOX[®] have not been established in pediatric patients. No pharmacokinetic data on SPORANOX[®] Capsules or Injection are available in children. A small number of patients ages 3 to 16 years have been treated with

100 mg/day of itraconazole capsules for systemic fungal infections, and no serious unexpected adverse effects have been reported. SPORANOX® Oral Solution (5 mg/kg/day) has been administered to pediatric patients (N=26, ages 6 months to 12 years) for 2 weeks and no serious unexpected adverse events were reported.

The long-term effects of itraconazole on bone growth in children are unknown. In three toxicology studies using rats, itraconazole induced bone defects at dosage levels as low as 20 mg/kg/day (2.5x MRHD). The induced defects included reduced bone plate activity, thinning of the zona compacta of the large bones, and increased bone fragility. At a dosage level of 80 mg/kg/day (10x MRHD) over 1 year or 160 mg/kg/day (20x MRHD) for 6 months, itraconazole induced small tooth pulp with hypocellular appearance in some rats. No such bone toxicity has been reported in adult patients.

Geriatric Use: Clinical studies of SPORANOX® Injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

SPORANOX® has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition. If clinical signs or symptoms develop that are consistent with liver disease, the risks and benefits of continued SPORANOX® use should be reassessed. (See WARNINGS: Hepatic Effects and PRECAUTIONS: Information for Patients.)

Adverse Events Reported in Trials in Patients with SPORANOX® Injection

Adverse events considered at least possibly drug related are shown in Table 2 and are based on the experience of 360 patients treated with SPORANOX® Injection in four pharmacokinetic, one uncontrolled and four active controlled studies where the control was amphotericin B or fluconazole. Nearly all patients were neutropenic or were otherwise immunocompromised and were treated empirically for febrile episodes, for documented systemic fungal infections, or in trials to determine pharmacokinetics. The dose of

SPORANOX® Injection was 200 mg twice daily for the first two days followed by a single daily dose of 200 mg for the remainder of the intravenous treatment period. The majority of patients received between 7 and 14 days of SPORANOX® Injection.

Table 2. Summary of Possibly or Definitely Drug-Related Adverse Events Reported by ≥2% of Subjects				
Adverse Event	Total SPORANOX® Injection (N=360) %	COMPARATIVE STUDIES		
		SPORANOX® Injection (N=234) %	Intravenous Fluconazole (N=32) %	Intravenous Amphotericin B (N=202) %
Gastrointestinal system disorders				
Nausea	8	9	0	15
Diarrhea	6	6	3	9
Vomiting	4	6	0	10
Abdominal pain	2	2	0	3
Constipation	0	1	3	0
Metabolic and nutritional disorders				
Hypokalemia	5	8	0	29
Alkaline phosphatase increased	1	2	3	2
Serum creatinine increased	2	2	3	26
Hypomagnesemia	1	1	0	5
Blood urea nitrogen increased	0	1	0	7
Fluid overload	0	0	0	3
Hypocalcemia	0	0	0	3
Liver and biliary system disorders				
Bilirubinemia	4	6	9	3
SGPT/ALT Increased	2	3	3	1
Hepatic function abnormal	1	2	0	2
Jaundice	1	2	0	0
SGOT/AST increased	1	2	0	0
Body as a whole – General disorders				
Pain	1	2	0	0
Rigors	0	0	0	34
Fever	0	0	0	6
Skin and appendages disorders				
Rash	3	3	3	3
Sweating increased	1	2	0	0
Respiratory system disorder				
Dyspnea	0	0	0	3
Central and peripheral nervous system disorders				
Dizziness	1	2	0	1
Headache	2	2	0	3
Urinary system disorders				
Renal function abnormal	1	1	0	11
Application site disorder				
Application site reaction	4	0	0	0
Cardiovascular disorders, general				
Hypotension	0	0	0	3
Hypertension	0	0	0	2
Heart rate and rhythm disorders				
Tachycardia	0	1	0	3
Vascular (extracardiac) disorders				
Vein disorder	3	0	0	0

The following adverse events occurred in less than 2% of patients in clinical trials of SPORANOX® Injection: LDH increased, edema, albuminuria, hyperglycemia, and hepatitis.

Post-marketing Experience

In worldwide post-marketing experience with SPORANOX® Capsules in treatment of onychomycosis and/or systemic fungal infections, peripheral edema, allergic reactions, including rash, pruritus, urticaria, angioedema, and, in rare instances, anaphylaxis and Stevens-Johnson syndrome, have been reported. Post-marketing experiences have also included reports of elevated liver enzymes and rarely liver failure. Rare cases of congestive heart failure and pulmonary edema have been reported. Rare cases of alopecia, hypertriglyceridemia, menstrual disorders, and neutropenia, and isolated cases of neuropathy have also been reported, although the causal association with SPORANOX® is uncertain. (See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.)

OVERDOSAGE

Itraconazole is not removed by dialysis.

There are limited data on the outcomes of patients ingesting high doses of itraconazole. In patients taking either 1000 mg of SPORANOX® (itraconazole) Oral Solution or up to 3000 mg of SPORANOX® Capsules, or b.i.d. dosing for four days with SPORANOX® Injection, the adverse event profile was similar to that observed at recommended doses.

DOSAGE AND ADMINISTRATION

Use only the components [SPORANOX® (itraconazole) Injection ampule, 0.9% Sodium Chloride Injection, USP (Normal Saline) bag and filtered infusion set] provided in the kit: **DO NOT SUBSTITUTE.**

SPORANOX® Injection should not be diluted with 5% Dextrose Injection, USP, or with Lactated Ringer's Injection, USP, alone or in combination with any other diluent. The compatibility of SPORANOX® Injection with diluents other than 0.9% Sodium Chloride Injection, USP (Normal Saline) is not known. **NOT FOR IV BOLUS INJECTION.**

NOTE: After reconstitution, the diluted SPORANOX® Injection may be stored refrigerated (2-8°C) or at room temperature (15-25°C) for up to 48 hours, when protected from direct light. During administration, exposure to normal room light is acceptable.

NOTE: Use only a dedicated infusion line for administration of SPORANOX® Injection. Do not introduce concomitant medication in the same bag nor through the same line as SPORANOX® Injection. Other medications may be administered after flushing the line/catheter with 0.9% Sodium Chloride Injection, USP, as described below, and removing and replacing the entire infusion line. Alternatively, utilize another lumen, in the case of a multi-lumen catheter.

Add the full contents (25 mL) of the SPORANOX® Injection ampule into the infusion bag provided, which contains 50 mL of 0.9% Sodium Chloride Injection, USP (Normal Saline). Mix gently after the solution is completely transferred. Using a flow control device, infuse 60 mL of the dilute solution (3.33 mg/mL = 200 mg itraconazole, pH apx. 4.8) intravenously over 60 minutes, using an extension line and the infusion set provided. After administration, flush the infusion set with 15-20 mL of 0.9% Sodium Chloride Injection, USP, over 30 seconds-15 minutes, via the two-way stopcock. Discard the entire infusion line.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Empiric Therapy in Febrile, Neutropenic Patients with Suspected Fungal Infections (ETFN): The recommended dose of SPORANOX® Injection is 200 mg BID for four doses, followed by 200 mg once daily for up to 14 days. Each intravenous dose should be infused over 1 hour. Treatment should be continued with SPORANOX® Oral Solution 200 mg (20 mL) BID until resolution of clinically significant neutropenia. The safety and efficacy of SPORANOX® use exceeding 28 days in ETFN is not known.

Treatment of Blastomycosis, Histoplasmosis and Aspergillosis: The recommended intravenous dose is 200 mg b.i.d. for four doses, followed by 200 mg q.d. Each intravenous dose should be infused over 1 hour.

For the treatment of blastomycosis, histoplasmosis and aspergillosis, SPORANOX® can be given as oral capsules or intravenously. The safety and efficacy of SPORANOX® Injection administered for greater than 14 days is not known.

Total itraconazole therapy (SPORANOX® Injection followed by SPORANOX® Capsules) should be continued for a minimum of 3 months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

SPORANOX® Injection should not be used in patients with creatinine clearance <30 mL/min.

HOW SUPPLIED

SPORANOX® (itraconazole) Injection for intravenous infusion is supplied as a kit (NDC 50458-298-01), containing one 25 mL colorless glass ampule of itraconazole 10 mg/mL sterile, pyrogen-free solution (NDC 50458-297-10), one 50 mL bag (100 mL capacity) of 0.9% Sodium Chloride Injection, USP (Normal Saline) and one filtered infusion set.

Store at or below 25°C (77°F). Protect from light and freezing.

SPORANOX® (ITRACONAZOLE) INJECTION

Distributed by:
Ortho Biotech Products, L.P.
Raritan, NJ 08869

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